

Treatment of Malignant Endocrine Pancreatic Tumors with a New Long-Acting Somatostatin Analogue, SMS 201-995

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Ten patients with malignant endocrine pancreatic tumors were treated with SMS 201-995 at doses of 50 µg twice daily, administered subcutaneously. Four out of 10 patients (40%)—1 patient with the Zollinger-Ellison syndrome and 3 of 6 with the watery diarrhea syndrome—responded objectively with more than 50% reduction of peptide levels, with a median duration of 15.5 months. All four patients improved symptomatically, with decreasing dyspeptic symptoms and decreasing diarrhoea. Three additional patients had a clear relief of symptoms without an effect on tumor-secreted peptides. The disease progressed in three patients during treatment. No reduction of tumor mass was seen in any of the patients. The main side effect noted was a slight but maintained increase in fasting blood glucose in four patients. In conclusion, SMS 201-995 had a beneficial effect in more than half of the patients and seems to be a valuable adjunct to other causal therapy in this patient category, especially in acute situations and weak patients because of its very few side effects.

Key words: Endocrine pancreatic tumors, malignant; somatostatin analogue SMS 201-995; tumor therapy

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Somatostatin is a naturally occurring peptide with a wide distribution in the body.

Because of its inhibitory effects, native somatostatin has been used therapeutically in various hypersecretory conditions in the gastrointestinal tract. In 1983 we could demonstrate the inhibition of tumor-secreted insulin and gastrin in a benign insulinoma and malignant gastrinoma (1). One disadvantage with native somatostatin is its short plasma half-life, only 2-3 min, which necessitates intravenous infusion (2). Another problem is the rebound phenomenon that occurs when the infusion is stopped (3).

A new long-acting somatostatin analogue, a cyclic octapeptide, SMS 201-995 (Sandoz, Basel, Switzerland) has recently become available (4).

It is more resistant to enzymatic degradation than the native compound, and its plasma half-life when given intravenously is approximately 60 min (5). It can also be administered subcutaneously, and its plasma half-life is then approximately 2 h (5). SMS 201-995 has been shown to be much more potent than the native compound, and it selectively suppresses growth hormone (GH) and glucagon levels more than insulin levels (5).

There are reports of beneficial effects of SMS 201-995 in cases of malignant endocrine pancreatic tumors (6-13), but the experience is still very limited. We thus want to report the effect of this long-acting somatostatin analogue in the management of 10 patients with malignant endocrine pancreatic tumors.

SUBJECTS AND METHODS

Patients

Ten patients, eight men and two women, with a mean age of 64.7 years (range, 50-75) were included in the study. Most of them had tumors with multiple peptide secretions; the peptide considered to be causing the syndrome was called the 'main' tumor. One patient had the Zollinger-Ellison syndrome, whereas six had the watery diarrhea syndrome. One patient had a malignant insulinoma, and the other two had no specific tumors—that is, they had no specific related symptoms. Two patients with the watery diarrhea syndrome had a MEN-1 trait. Seven patients had a remaining pancreatic tumor, and eight had metastases. One patient had lung metastases.

Five patients had been subjected to surgery. Embolization of liver metastases had been undertaken in one case. Seven patients had received chemotherapy, mainly streptozocin, 5-fluorouracil or doxorubicin (1-4), with initial responses but then failed to maintain treatment. These seven patients had been treated with human leukocyte interferon with responses of various duration but progressive disease when SMS 201-995 started. Two patients had received surgery, and therapy with SMS 201-995 was started because of their poor general condition, making chemotherapy and interferon treatment impossible.

Methods

Fasting peripheral blood samples were collected before and during SMS 201-995 treatment. Insulin, proinsulin, c-peptide, gastrin, chorionic gonadotropin (HCG), growth hormone (GH), growth hormone releasing hormone (GRH), subunits (15), pancreatic polypeptide (PP), calcitonin (17), plasma vasoactive intestinal peptide (VIP) (18), glucagon (19), and neurotensin (21) were measured by radioimmunoassays described elsewhere (15). Hematology, liver enzymes, blood glucose, T₄, and thyroid-stimulating hormone (TSH) assays were checked before and during treatment. Histopathologic diagnosis was made by light microscopy.

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tumors were treated with SMS 201-995 subcutaneously. Four out of 10 patients had the watery diarrhea and 3 of 6 with the watery diarrhea had more than 50% reduction of peptide secretion. All four patients improved symptoms and decreasing diarrhoea. Three without an effect on tumor-secreted hormones during treatment. No reduction of the main side effect noted was a slight decrease in insulin levels. In conclusion, SMS 201-995 is a potent somatostatin analogue in the treatment of the patients and seems to be a new treatment category, especially in acute watery diarrhea.

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to enzymatic degradation than native, and its plasma half-life is approximately 60 min after subcutaneous administration. Its half-life is then approximately 2 h. It has been shown to be much more stable than the native compound, and it is as potent as growth hormone (GH) and as effective as insulin levels (5).

of beneficial effects of SMS 201-995 on malignant endocrine pancreas, but the experience is still limited. We want to report the effect of SMS 201-995 in the treatment of patients with malignant endocrine tumors.

SUBJECTS AND METHODS

Patients

Ten patients, eight men and two women, with a mean age of 64.7 years (range, 54-73 years) were included in the study. Most of the patients had tumors with multiple peptide secretion, but the peptide considered to be causing the clinical syndrome was called the 'main' tumor marker. One patient had the Zollinger-Ellison syndrome, whereas six had the watery diarrhea (WDHA) syndrome. One patient had a malignant insulinoma, and the other two had non-functioning tumors—that is, they had no specific hormone-related symptoms. Two patients with the WDHA syndrome had a MEN-1 trait. Seven patients had a remaining pancreatic tumor, and eight had liver metastases. One patient had lung metastases.

Five patients had been subjected to pancreatic surgery. Embolization of liver metastases had been undertaken in one case. Seven patients had received chemotherapy, mainly streptozocin plus 5-fluorouracil or doxorubicin (Adriamycin®), with initial responses but then failure of this treatment. These seven patients had also been treated with human leukocyte interferon with responses of various duration but were showing progressive disease when SMS 201-995 was started. Two patients had received no prior treatment, and therapy with SMS 201-995 was started because of their poor general condition, which made chemotherapy and interferon treatment impossible.

Methods

Fasting peripheral blood samples were collected before and during SMS therapy. Serum insulin, proinsulin, C-peptide, gastrin (14), human chorionic gonadotropin (HCG) alpha and beta subunits (15), pancreatic polypeptide (PP) (16), calcitonin (17), plasma vasoactive intestinal polypeptide (VIP) (18), glucagon (19), somatostatin (20), and neurotensin (21) were analyzed by radioimmunoassays described earlier. Routine hematology, liver enzymes, blood glucose, serum T₄, and thyroid-stimulating hormone (TSH) assays were checked before and regularly during treatment. Histopathologic diagnosis was estab-

lished in all 10 cases on tissue specimens taken at surgery or by coarse-needle biopsy (22). All tumors were argentaffinophilic with the Grimelius silver nitrate stain (23). Routinely fixed, paraffin-embedded sections were immunohistochemically investigated with antibodies against gastrin, insulin, PP, glucagon, somatostatin, HCG alpha, HCG beta, calcitonin, VIP, and neurotensin (24).

SMS 201-995

SMS 201-995, the long-acting cyclic octapeptide produced by Sandoz, was administered as daily subcutaneous injections at initial doses of 50 µg twice daily. In seven of the patients increased doses were required.

Evaluation of tumor response

In the evaluation of the therapeutic effect, *objective response* was defined as a reduction of the 'main' tumor markers and/or tumor size by >50%. *Stable disease* was defined as a reduction of the main tumor marker and/or tumor mass by <50% and no appearance of new metastases. *Progressive disease* was defined as an increase in tumor markers and/or tumor mass by >25% or appearance of new metastases.

RESULTS

Objective responses were seen in 4 of 10 patients (40%) treated with SMS 201-995 (Table I). The mean duration of the response was 13.5 months (median, 15.5 months; range, 5-18 months). All four patients had a reduction of the main tumor marker by more than 50% (one patient with the Zollinger-Ellison syndrome and three of six with the WDHA syndrome). No patient had a reduction of tumor mass. However, tumor size remained unchanged on computed tomography (CT) scans in all patients during the observation time (mean, 9 months). Three patients had stable disease with a mean duration of 4.3 months. In three of the patients with objective response and in two of the patients with stable disease the somatostatin dose was increased up to 200 µg/day within 2-14 months to maintain the effect. Progressive disease was noted in the other three patients.

Symptomatically, 7 of the 10 patients (70%)

Table 1. Patients with malignant endocrine pancreatic tumors treated with SMS 201-995

| Patient no. | Clinical syndrome* | Earlier treatment† | Duration of disease | SMS treatment: hormone levels‡ | | Duration of therapy | Duration of objective response | Sympt. effect | Adverse effect |
|-------------|--------------------|--------------------|---------------------|--------------------------------|-------------|---------------------|--------------------------------|---------------|-------------------------------|
| | | | | Before | After | | | | |
| 1 | Z-E | CT; IFN | 120 mo | Gastrin, 194 pmol/l | 35.3 pmol/l | 18 mo | 18 mo | + | Slight diabetes |
| 2 | WDHA | CT; IFN | 32 mo | No measurable marker | | 6 mo | — | + | Abd. pain + fever |
| 3 | WDHA | CT; IFN | 38 mo | Calc., 18,000 ng/l | 9000 ng/l | 16 mo | 16 mo | + | Higher insulin dose |
| 4 | Non-f | None | 120 mo | Calc., 420 ng/l | 660 ng/l | 19 mo | — | + | Slight diabetes |
| 5 | WDHA | CT; IFN | 84 mo | PP, 14.2 ng/l | 7.0 ng/l | 5 mo | 5 mo | + | Slight diabetes |
| 6 | WDHA | CT; IFN | 156 mo | Calc., 470 ng/l | 180 ng/l | 15 mo | 15 mo | + | Slight diabetes, hypocalcemia |
| 7 | WDHA | None | 4 mo | VIP, 190 pmol/l | 190 pmol/l | 2 mo | — | — | — |
| 8 | Hypoglycemia | None | 2 mo | Insulin, 129 mU/l | 102 mU/l | 2 days | — | — | Lower b-glucose |
| 9 | Non-f | CT; IFN | 36 mo | PP, 1.85 ng/ml | 2.7 ng/ml | 1 mo | — | — | — |
| 10 | WDHA | CT; IFN | 76 mo | VIP, 37.6 | 73.8 | 6 mo | — | + | Abd. pain + fever |

* Z-E = Zollinger-Ellison; WDHA = water diarrhea hypokalemia achlorhydria; non-f = non-functioning tumor.

† CT = chemotherapy; IFN = human leukocyte interferon.

‡ Calc = calcitonin; PP = pancreatic polypeptide; VIP = vasoactive intestinal polypeptide.

improved. As is shown in Table 1, five patients with the WDHA syndrome, one with the Zollinger-Ellison syndrome, and one with a non-functioning tumor responded subjectively.

One of the patients who did not respond had a VIPoma, which also produced large amounts of endogenous somatostatin. In this case we attempted doses as high as 100 µg/h intravenously without achieving an effect.

In the four patients with objective response, all with multiple peptide secretion, the main marker decreased, while the other peptides increased. There was a discrepancy in the inhibiting effect on the release of different peptides.

Another observation could be made in two patients (cases 3 and 4), whose tumors had no known production of gastrin. During treatment with SMS 201-995 serum gastrin levels increased in both, while the tumor markers decreased. Basal acid output was measured in one of them and was shown to be very low.

Adverse effects

The side effects with this somatostatin analogue are remarkably few. We noticed a slight increase in fasting blood glucose (1.8 ± 1.1 (SD) mmol/l) in 4 of the 10 patients (Table 1). One patient with insulin-treated diabetes required a higher insulin dose. Another patient with a malignant insulinoma received SMS 201-995 during the first 24 h in hospital, but blood glucose levels rather decreased, and alternative treatment had to be initiated. No patient developed clinically significant diarrhea or steatorrhea, probably because we used a relatively low dosage and because eight patients received pancreatic enzymes prophylactically. The existence of a subclinical malabsorption or steatorrhea cannot be excluded, since fat excretion was not routinely measured. Two patients with the WDHA syndrome, both of whom had been subjected to extensive abdominal surgery (in one case by the method of Whipple), developed abdominal pain and fever attacks, which were interpreted as attacks of cholangitis. Decreased intestinal motility caused by the analogue could explain these attacks. In both patients SMS 201-995 was withdrawn, and in one the adverse symptoms decreased within 3 days, and

SMS 201-995 could be reinitiated in a low dose. Pain at the injection site was a problem in patients who received higher doses.

One patient with MEN-1 and the WDHA syndrome was maintained on a low substitution of calcium after surgery for hyperparathyroidism and developed severe hypocalcemia (reference level, 2.20–2.60) 3 months after initiation of SMS, and vitamin D substitution was added. Parathyroid hormone (PTHrP) remained unchanged. The hypocalcemia in this patient could reflect intestinal inhibition of calcium absorption by the analogue, or the hormone or liver enzyme values or the radiology results were not altered by the treatment.

DISCUSSION

The optimal treatment in malignant pancreatic tumors has not yet been established. Surgery is the primary form of treatment, but because most patients have inoperable disease, other forms of treatment should be considered. Chemotherapy produces responses in >60% of patients with malignant pancreatic tumors (EORTC trial). The median duration of response of 17 months with Human leukocyte interferon has been shown to give objective responses in patients with malignant EPT, with a duration of 8.5 months (27). However, the treatments cure the disease, and further treatments are needed.

There are already several reports of beneficial effects of SMS 201-995 in patients with malignant EPT. Improvement in reduction of peptide levels, and, in some cases, reduction of tumor mass have been observed (12).

In our study SMS 201-995 was used in patients with advanced disease, where cytotoxics and interferon no longer had any effect. In two patients the somatostatin analogue was the only treatment that the patients tolerated because of their poor clinical condition.

In more than half of our patients SMS 201-995 had a beneficial effect, with subjective responses in seven patients.

shown in Table I, five patients with the Zollinger-Ellison syndrome, one with the Zollinger-Ellison syndrome, and one with a non-responded subjectively.

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Comparison could be made in two patients (nos. 3 and 4), whose tumors had no effect of gastrin. During treatment of gastrin. During treatment serum gastrin levels increased and other markers decreased. Basal gastrin was in one of them and was low.

With this somatostatin analogue we noticed a slight increase in gastrin (1.8 ± 1.1 (SD) mmol/l) (Table I). One patient with diabetes required a higher insulin dose with a malignant insulinoma. SMS 201-995 during the first 24 h did not affect glucose levels rather than native treatment had to be given. The developed clinically significant diarrhea, probably because of low dosage and because eight pancreatic enzymes prophylactically of a subclinical malabsorption cannot be excluded, since it is routinely measured. Two patients with DHA syndrome, both of them led to extensive abdominal pain by the method of Whipple). The pain and fever attacks. The attacks of cholangitis. The motility caused by the analgesic attacks. In both patients the analgesic was withdrawn, and in one the pain ceased within 3 days, and

SMS 201-995 could be reinitiated in an escalating dose. Pain at the injection site was a complaint in patients who received higher doses.

One patient with MEN-1 and the WDHA syndrome was maintained on a low substitution dose of calcium after surgery for hyperparathyroidism and developed severe hypocalcemia (1.61 mmol/l; reference level, 2.20–2.60) 3 months after initiation of SMS, and vitamin D substitution therapy was added. Parathyroid hormone (PTH) levels remained unchanged. The hypocalcemia in this patient could reflect intestinal inhibition of calcium absorption by the analogue. Thyroid hormone or liver enzyme values or routine hematology results were not altered by the treatment.

DISCUSSION

The optimal treatment in malignant endocrine pancreatic tumors has not yet been established. Surgery is the primary form of treatment (25), but because most patients have inoperable metastasizing disease, other forms of therapy have to be considered. Chemotherapy produces objective responses in >60% of patients with malignant endocrine pancreatic tumors (EPT) with a median duration of response of 17 months (26). Human leukocyte interferon has recently been shown to give objective responses in 77% of patients with malignant EPT, with a median duration of 8.5 months (27). However, none of the treatments cure the disease, and alternative treatments are needed.

There are already several reports about the beneficial effects of SMS 201-995 in the treatment of malignant EPT. Improvement of symptoms, reduction of peptide levels, and, in isolated cases, reduction of tumor mass have been described (6–12).

In our study SMS 201-995 was attempted in 10 patients with advanced disease, in which both cytotoxics and interferon no longer had an effect. In two patients the somatostatin analogue was the only treatment that the patients could tolerate because of their poor clinical condition.

In more than half of our patients the treatment had a beneficial effect, with symptomatic and subjective responses in seven patients. In 4 out of

10 patients (40%) SMS 201-995 reduced the levels of tumor-produced peptides by more than 50%, with a median duration of 15.5 months. However, with time higher doses seemed to be required to keep the peptide levels down and clinical symptoms away. Six patients required a dose increase after 2–14 months of up to 200 µg/day. The patients seem to develop tachyphylaxis, which might be due to down-regulation of somatostatin receptors. In one patient with a somatostatin-producing VIPoma, 100 µg/h intravenously was tried without any effect. The therapy resistance in this particular case should be noted, since concomitant somatostatin production from a tumor probably down-regulates somatostatin receptors. This mechanism for therapy resistance to SMS 201-995 has not been reported earlier. The observation that symptomatic improvement persisted in spite of increasing peptide levels or occurred without accompanying decrease in tumor markers has also been made by others (12). This discrepancy between objective and symptomatic response could reflect the proportionally stronger and longer-lasting effect of SMS 201-995 on peripheral target organs—that is, the mucosa of the stomach and the intestine described in earlier reports (10). The increase in serum gastrin in two of our patients during treatment could also be an expression of this phenomenon. Decreased basal acid output was demonstrated in one of these two patients but not measured in the other.

Whether SMS 201-995 has an effect on tumor growth is still not known. In the present study no patient had a reduction of tumor mass. On the other hand, no increase in tumor size was seen on CT scan, which could indicate an inhibitory effect on tumor cell growth. In animal models, SMS 201-995 has been reported to have moderate but significant inhibitory effects on the growth of transplanted peptide-producing tumors (28). There have been reports in the literature about possible shrinkage of metastases of EPT during treatment with SMS 201-995 (13), but these observations need confirmation in additional studies of patients. Since SMS 201-995 does not exert cytostatic effects, the inhibited growth might be due to inhibition of autocrine and/or endocrine growth factors.

The optimal dose of the analogue is not yet clear. We have used a relatively low dose compared with others, and higher doses might improve the results. We attempted higher doses in some of our patients, and they tolerated these doses well (100 µg/h intravenously). SMS 201-995 has relatively few adverse effects. The occurrence of steatorrhea, an observed side effect in other reports (29), was not thoroughly studied in this patient material. Hypocalcemia, attacks of cholangitis, and the worsening of hypoglycemia seen in the insulinoma patient deserve mention.

In conclusion, the analogue seems to have dual effects, acting both directly on tumor-produced peptide release and indirectly on the peripheral target organs of the peptides. Even though some patients do not respond objectively to the treatment, there may be a beneficial and ameliorating effect on peptide-related symptoms, which is an important goal in the treatment of this patient category. In the management of patients with malignant endocrine pancreatic tumors, SMS 201-995 will probably be a valuable complement to chemotherapy and interferon treatment, especially in acute stages of the disease and in elderly, weak patients because of its very few side effects.

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